National Stroke Project – Transient Ischemic Attack/Ischemic Stroke
Clinical Background

When considered separately from other cardiovascular diseases, stroke is reported to be the third leading cause of death in the United States, as well as a leading cause of serious, long-term disability. According to the American Heart Association, approximately 600,000 people suffer an initial (500,000) or recurrent (100,000) stroke annually in the United States, and it has been estimated that carotid artery disease may be responsible for 20 to 30 percent of them. For people over age 55, the incidence of stroke more than doubles in each successive decade. About 29 percent of people who have an initial stroke die within a year. This percentage is higher among people age 65 and older. [3]

Frequently, carotid artery stenosis is diagnosed after a transient ischemic attack (TIA) or stroke, but for some two to five percent, cerebral infarction caused by embolism or carotid occlusion is the initial event. [9] The majority of strokes are ischemic with approximately 30 percent resulting from atherothrombosis in extracranial and larger intracranial vessels and another 20 to 25 percent from cardiac emboli due to atrial fibrillation or myocardial infarction. [15] Among the risk factors for TIA or stroke, the most important is a prior TIA or stroke, each of which carries a tenfold increase in risk. In addition, the presence of atrial fibrillation represents an increase in risk by six times. [15] In general, patients with TIAs related to severe carotid stenosis are at risk for stroke at a rate of 12 to 13 percent within the first year after symptoms begin, with a cumulative stroke risk of 30 to 35 percent at the end of five years.

Other factors strongly related to stroke risk include hypertension (one of most important stroke risk factors based on degree of risk and prevalence), cardiac morbidity, smoking, diabetes, physical inactivity and high levels of alcohol consumption. [77] The Renfrow/Paisley cohort study in Scotland offers further insight into the associations between risk factors and stroke incidence and mortality. In the early to mid-1970s, when they were 45 to 64 years of age, 7,052 men and 8,354 women were screened for risk factors. These factors were related to stroke incidence over 20 years of follow-up. Blood pressure (both diastolic and systolic), smoking, cardiothoracic ratio, preexisting coronary heart disease and diabetes were positively related to stroke incidence, while forced expiratory volume and height were negatively related. Interestingly, former smokers had similar stroke rates to never-smokers. These risk factors had a similar effect on stroke mortality. [73]

Data for Americans 40 years old and older showed the average in-hospital and physician costs were $11,010 for a stroke and $4,940 for TIA in 1995. [19] According to data from the Health Care Financing Administration, $3.7 billion ($5,718 per discharge) was paid for Medicare beneficiaries with stroke in 1995. [3] Costs have been found to be higher for patients with recurrent stroke than for those with an initial stroke. [61] Researchers supported by the Agency for Health Care Policy and Research (AHCPR) found that expanded and appropriate use of the anticoagulant warfarin could cut in half the 80,000 strokes each year due to atrial fibrillation and could save approximately $600 million annually. [15]

Antithrombotic Therapy

Antithrombotic drugs are an important part of the care of patients with ischemic stroke because it is largely due to embolic or thrombotic arterial occlusion. These drugs may prevent deterioration of the condition, improve the potential for recovery by forestalling recurrent embolism, halt reproduction of a thrombus, and/or assist in the maintenance of blood flow through collateral channels. [2]

Medical treatments for stroke prevention include anticoagulation and antiplatelet therapy. [7- 9, 11, 12, 15, 16, 18, 27-32, 47,48,49, 60, 71, 79] Warfarin for patients with non-valvular atrial fibrillation is one of the most well-studied treatments for stroke prevention as supported in Matchar et al. [15] and the Stroke Prevention in Atrial Fibrillation (SPAF), [7,11] Atrial Fibrillation, Aspirin and Antikoagulation (AFASAK), [16] Canadian Atrial Fibrillation Anticoagulation (CAFA), [12] European Atrial Fibrillation Trial (EAFT) [13] and Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) [18] studies.
The relative risk reduction of ischemic stroke in these studies for patients receiving warfarin with atrial fibrillation is significant, ranging from 37 to 86 percent.

The use of aspirin, warfarin, or ticlopidine [20] for prevention of TIA and ischemic stroke has been the subject of multiple studies, including the Swedish Aspirin Low-dose Trial (SALT), [8] and has been shown to reduce the risk of recurrent stroke in patients with completed minor strokes, as well as in patients with previous TIAs. The dose of aspirin required for stroke prevention in persons with cerebrovascular disease has been a subject of debate among stroke neurologists. Meta-analyses of trials at different dose ranges strongly suggest that the benefit of aspirin is independent of dose. [60,79] Ticlopidine has been shown to be effective for both primary and secondary stroke prevention with a favorable risk/benefit ratio. [46] One study found ticlopidine was more effective than aspirin but was less well tolerated and was associated with severe but reversible neutropenia in almost 1 percent of patients. [29] In addition, the immediate effects of 325 mg of aspirin on platelet aggregation suggest that it would be useful in acute stroke [4] much the same way it is used in acute myocardial infarction. Aspirin is clearly not a suitable substitute for warfarin in patients with non-valvular atrial fibrillation who have experienced a recent stroke or TIA. [15] In the EAFT, an 11 percent rate of stroke in patients receiving aspirin was reduced by seven percent per year in the warfarin-treated group. [15]

Two additional drugs approved for use in stroke prevention are clopidogrel [46] and dipyridamole alone and in combination with aspirin.[47] The trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE) found that patients treated with clopidogrel had an annual 5-32 percent risk of ischemic stroke, myocardial infarction or vascular death compared with 5-83 percent with aspirin. This translates to a statistically significant relative risk reduction of 8.7 percent in favor of clopidogrel over aspirin. Authors concluded that clopidogrel is at least as safe as medium-dose aspirin and is safer than ticlopidine. In a more recent examination of data from the CAPRIE trial, the effect of clopidogrel on the high rate of ischemic events (i.e., angina, TIA, severe limb ischemia) leading to hospitalization for patients with atherosclerotic disease was examined. Hospitalization related to hemorrhage was also studied. The authors concluded that treatment with clopidogrel results in a significant decrease in the need for rehospitalization for ischemic events or bleeding when compared with aspirin (1,502 compared to 1,673, p=.010). [54]

In June 2000, the *New England Journal of Medicine* published the results of a study linking thrombocytopenic purpura with the initiation of clopidogrel, often within the first two weeks of treatment. The authors reported on 11 patients who developed thrombotic thrombocytopenic purpura during or soon after treatment with clopidogrel. Ten of the 11 patients had received clopidogrel for two weeks or less before the onset of this condition. Most of these patients responded to plasma exchange, although two required multiple exchanges. There was one death. Physicians were warned to be aware of the possibility of this syndrome when initiating clopidogrel treatment. [64]

The second European Stroke Prevention Study (ESPS-2) showed a substantial benefit for dipyridamole combined with aspirin over aspirin alone. When the ESPS-2 data were aggregated with the 14 previous trials of dipyridamole combined with aspirin over aspirin alone, the combination was found to reduce the risk of stroke by 23 percent over aspirin alone.

Although heparin is the most commonly prescribed antithrombotic drug, evidence about its efficacy and safety is limited. Data addressing heparin's role in acute stroke management are conflicting and studies have been insufficient leading to confusion regarding: the best dosing level, route, timing and duration of treatment, use of a bolus dose, what severity of neurological deficits is appropriate for heparin use, and influence of vascular distribution and/or cause of the stroke that would contraindicate its use. [1]

A recent study examined the use of low molecular-weight (LMW) heparin compared with aspirin in patients with acute ischemic stroke. [67] The goal was to test whether treatment with LMW heparin started within 30 hours of stroke onset is superior to aspirin in the prevention of recurrent stroke during the first two weeks. There were no significant differences in functional outcome or death at 14 days or three months leading the authors to conclude that the present data do not provide evidence that LMW heparin is superior to aspirin for prevention of recurrent stroke. [67]

Rapid-acting Antihypertensives

The use of rapid-acting antihypertensives with acute ischemic stroke is addressed by the 1994 American Heart Association Guidelines for the Management of Acute Ischemic Stroke. [1] The authors determined that, in general, antihypertensive drugs should be withheld unless the calculated mean blood pressure is greater than 130 mm Hg or the systolic blood pressure is greater than 220 mm Hg. In particular, they warn that the sublingual use of nifedipine may cause further tissue damage due to its rapid absorption, which could lead to a secondary precipitous drop in blood pressure. [1] They further suggest that most patients with acute stroke do not need treatment with parenteral antihypertensives, and that oral drugs are preferred. For patients with extreme elevations of blood pressure that do require parenteral therapy, they recommend drugs that are easily titrated and have minimal effects on cerebral vessels. Examples are labetolol and enalapril.

These findings are supported by a more recent publication that discusses the use of anithypertensive therapies in patients with acute ischemic stroke. The authors warn against the use of sublingual calcium antagonists that have the capacity to cause a precipitous decline in blood pressure. [51] Messerli et al. were the first to caution against the use of sublingual nifedipine as a drug to lower blood pressure rapidly. [39] While this publication attracted some attention, the same group's article in *JAMA* reached a much wider audience. [14] They cite 40 articles recommending the use of sublingual

nifedipine for hypertensive emergencies. But they point out the following:

- sublingual absorption of nifedipine is poor
- most of the drug, when given sublingually is absorbed from the intestine
- standardized dosing is difficult with sublingual delivery
- there are no outcome studies to support the efficacy of this method of administration.

The authors also cite eight articles with 16 cases in which nifedipine administered sublingually resulted in fetal distress or cardiac or cerebrovascular complications from hypotension. In addition, the authors report that the FDA considered sublingual nifedipine for hypertension in the early 1980s and rejected its use for that indication. The admonition on nifedipine is specifically for the short-acting form of the drug and its administration by the sublingual route.

The Physicians' Desk Reference [40] now contains a bold-faced warning that nifedipine should not be used for acute reduction of blood pressure or for control of essential hypertension. A recent review on the treatment of stroke states that the use of sublingual nifedipine is inappropriate. [41]

A meta-analysis of 98 studies with 5,198 exposures to nifedipine for hypertension found serious cardiovascular side effects in less than 1 percent of exposures, a rate half that of the controls. [42] There was one stroke reported in the nifedipine-treated patients, and four in controls. Since 91 percent of the monotherapy exposures, and an unreported but presumable high percentage of the combination therapy exposures were to sustained or extended release forms of the drug, the authors' conclusions about the safety of the drug are confined to the sustained release form. The review was also limited to studies of mild to moderate hypertension.

The relationship between elevated blood pressure and intracranial bleeding following thrombolytic therapy is not well defined but uncontrolled arterial hypertension is considered a contraindication for the emergent use of thrombolytics. [5] Minimal or no treatment of mildly to moderate elevated blood pressure during the first hours of the ischemic stroke is supported by human and animal data. Most patients with ischemic stroke who have elevated blood pressure during the first several hours after stroke onset have a spontaneous decline in elevated blood pressure without antihypertensive medication. [26]

CT/MRI

An early imaging study is standard of care. According to Adams et al., computed tomography (CT) of the brain provides a means of effectively discriminating between ischemic and hemorrhagic stroke, an important initial step since the clinical signs and symptoms are similar while the therapy is quite different. [1] CT scans can also identify nonvascular lesions such as brain tumors, which can produce focal neurological signs. Though this non-invasive test can miss a subtle subarachnoid hemorrhage, the effectiveness of early CT in detecting intracerebral hemorrhage is nearly 100 percent. [1] CT of the head also has a role in the evaluation of patients with TIA, traditionally thought to represent reversible ischemia without infarction, because it may detect a cerebral infarction with short-lived symptoms. [6] Silent cerebral infarction (stroke without a symptomatic history) has been identified in 13 percent of patients with TIA and in 47 percent of patients with TIA in conjunction with carotid stenosis. [6]

A Canadian study explored the use of a CT score to assist in identifying stroke patients who are unlikely to make an independent recovery despite thrombolytic treatment. This study included a total of 203 consecutive patients with ischemic stroke who were treated with intravenous alteplase within three hours of symptom onset. All pretreatment CT scans were prospectively scored using a process that divided the middle cerebral artery territory into ten regions. Ischemic changes on the baseline CT scans were seen in 117 (75 percent) of 156 treated patients with anterior circulation ischemia. Baseline CT scores correlated inversely with the severity of stroke on the National Institutes of Health Stroke Scale. [62]

In contrast, magnetic resonance imaging (MRI) is more sensitive than CT for detection of cerebral ischemic infarction within the first 24 hours of onset, for early documentation of hemorrhagic infarction, and to show early signs of post-infarction brain edema and mass effect. Its limitations include higher cost, less availability, decreased resolution of early intracranial hemorrhage compared to CT, and claustrophobic reactions. [6]

Research is currently underway to determine if diffusion-weighted MRI (DWI) increases the accuracy of acute ischemic stroke identification. For example, a recent prospective study compared the yield of adding DWI to a conventional MRI protocol for acute stroke. A total of 52 patients with a clinical diagnosis of acute stroke presenting within 48 hours of symptom onset were included. Conventional MRI correctly identified at least one acute lesion in 71 (34/48) to 80 percent (39/49) of patients who had an acute stroke. With the addition of DWI, this percentage increased to 94 percent (46/49). [72] Another recent study explored the use of DWI with TIA and concluded that the addition of this technology increases the opportunity to identify the development of an infarct despite transient symptoms. [80]

Thrombolytic Therapy

The possibility of thrombolytic therapy for stroke is highly attractive. Enthusiasm for it must be countered by the potential for intracerebral hemorrhage in the ischemic area or elsewhere in the brain.

A large multi center clinical trial, the National Institute of Neurological and Stroke rt-PA Stroke Study Group (NINDS), was published in 1995. [33] This study used two different outcome measures. The study was divided into Part 1, with 291 patients randomized with the outcome measured on the NIH stroke scale. Part 2 randomized 333 patients using as an outcome measure a global test statistic that incorporated scores of four measures of stroke. This study required that recombinant tissue plasminogen activator (rt-PA) be administered within three hours of onset of symptoms, using 0.95mg/kg as a dose of rt-PA after determining from dose escalation studies that this was safe. In Part 1, with the single outcome measure, there was no difference in 24 hours, but the treatment group did better on the NIH scale when measured after three months. When the global test of four outcome measures was applied retrospectively to this group, there was improvement in all four measures at three months. When the outcome test was applied prospectively in Part 2, the treatment arm showed benefit on all four measures at three months with an odds ratio of 1.7 (statistically significant). They were also 30 percent more likely to have no disability at three months. Balancing the findings was a rate of symptomatic intracerebral hemorrhage in 6.4 percent in the treatment arm, but a rate of only 0.6 percent in the control arm.

The benefit accrued for all types of stroke -- small-vessel occlusive, large-vessel occlusive and cardioembolic. The benefit remained when results were adjusted for age, severity of stroke and use of aspirin prior to the stroke. While there was a 10-fold higher incidence of symptomatic hemorrhage in the treatment arm (20 vs. two) the overall outcome benefit outweighed the increased risk of stroke.

The first ECASS (European Cooperative Acute Stroke Study) investigation was published about the same time. [34] This was a smaller study, with slightly more than 600 randomized patients. They entered patients up to six hours after onset of symptoms and treated with a higher dose of rt-PA, (1.1 mg/kg). In analyzing those patients who completed the protocol, they found benefit in treated patients who had moderate to severe deficits without extended signs of infarct on CT. However, of the 620 patients, 109 were excluded for protocol violations. Two-thirds of the excluded patients were in the treatment arm. When the excluded patients were added back for intention-to-treat analysis, the benefit of rt-PA disappeared. The study also had higher rates of mortality and intracerebral hemorrhage than the NINDS study. These suggest that ECASS patients were less highly selected than the NINDS study patients. A partial explanation for these drawbacks may be the larger number of institutions participating in the ECASS study (75 vs. nine) resulting in more difficulty in protocol adherence.

The investigators corrected many of these weaknesses in ECASS II. [35] This study randomized 800 patients who were analyzed on an intention-to-treat basis. The dose of rt-PA was lowered to 0.9 mg/kg. They found no difference in the three-month outcome between the placebo and treatment arms. When the patients were stratified to treatment at zero to three hours and three to six hours after onset, there was still no difference. There was no difference in mortality in the two groups, about 10 percent for each. Symptomatic cerebral hemorrhage occurred in 8.8 percent of the treatment arm and 3.4 percent of the placebo arm. Only in a post-hoc analysis of death and dependency, was there a significant benefit for the treatment arm. Analyzed in terms of absolute numbers, in the treatment arm, about 40 more patients had benefit as measured on the single post-hoc outcome of dependency, while 20 more had symptomatic intracranial hemorrhage. Additionally, there were no benefits on the more comprehensive a priori outcome measure.

The NINDS and ECASS studies yielded a number of subsequent articles from post hoc analyses:

- In the NINDS study, analyses of patient factors such as age, presence of diabetes, congestive heart failure, atherosclerosis or hypertension, stroke severity and early CT findings did not alter the likelihood of responding favorably to rt-PA therapy. [43]
- In the NINDS study, treatment with thrombolysis was examined for potential cost-savings. [36] Length of stay was shorter and more patients were discharged home in the rt-PA group. Modeling based on these and other factors suggest that treatment with rt-PA will be more cost-effective. Higher costs associated with drug costs, ICU time and treatment of hemorrhage are offset by lower costs for rehabilitation and long term care. The cost savings were not accounted for by the early deaths from hemorrhage in the treated group.
- Based on data from the NINDS study, a more detailed analysis of the 22 patients with symptomatic intracerebral hemorrhage was published. [37] Greater severity of neurological deficit and brain edema increased the risk of hemorrhage in the rt-PA group. However, the numbers were small, the confidence intervals wide and the model had limited application. Ninety percent of the hemorrhages occurred within 24 hours after treatment was started. After 36 hours, the incidence of hemorrhage was the same in treated and control patients.

- Data from the placebo arms of parts one and two of the NINDS tPA trial were used to identify variables that could predict a poor outcome (moderately severe disability, severe disability or death) three months after stroke. The goal of this study was to develop models for clinicians to use to predict which patients with acute ischemic stroke might be at high risk for severe disability or death in the absence of thrombolytic therapy. Clear answers were not provided by this study and further research is needed in this area. [55]
- In the NINDS trial a total of 624 patients with stroke were randomly assigned to receive either tPA or placebo. Outcome data were collected over one year after the occurrence of stroke. The patients treated with tPA were at least 30 percent more likely to have minimal or no disability than were placebo treated patients but there was no difference in mortality between the two groups at one year. These results indicate a sustained benefit of tPA for such patients. [63)]
- The ECASS investigators analyzed the factors in predicting hemorrhage. [38] They also found severity of initial deficit, presence of early ischemic changes on CT and age were among the predictors. Interestingly, the strongest predictor was treatment with rt-PA.

There are pending studies with other selection criteria, different time windows and other agents. Additional information on the use of thrombolysis can be expected in the next few years.

A review of the thrombolytic trials to date was conducted to assess the safety and efficacy of thrombolytic agents in patients with acute ischemic stroke. Seventeen trials (5,216 patients) were included in the review. Fifteen of the trials were double-blinded and about 50 percent of the data came from trials using intravenous administration (two trials used an intra-arterial route). The reviewers found that despite a significant increase in the odds of death within the first ten days after thrombolytic therapy, patients receiving a thrombolytic within six hours of an ischemic stroke were less likely to die or remain disabled at the end of follow-up. Additional trials are needed to identify which patients are most likely to benefit from treatment and which treatment environments are best, before thrombolytic therapy is adopted on a wider scale. [59]

Studies regarding the use of tPA in clinical practice have been underway since the trial results were published. Results seem to indicate that favorable outcomes are achievable but that protocol violations are problematic. The violations expose patients to undue risk and indicate the need for further physician education and focused system changes. It is only with careful patient selection, individualized therapy according to the causative lesion, strict adherence to treatment guidelines, and evidence-based therapeutic decision-making by physicians with experience using these agents that patients will derive optimal benefit. [76]

- Results from the Standard Treatment with Alteplase to Reverse Stroke (STARS) study were published in March 2000. This prospective, multicenter study included 389 consecutive patients enrolled between February 1997 and December 1998 in 57 medical centers in the United States. STARS was designed to assess the safety profile and document clinical outcomes and adverse events in patients treated with intravenous tPA for acute stroke. Median time from stroke onset to treatment was two hours, 44 minutes and the median National Institutes of Health Stroke Scale score was 13. At 30 days, 35 percent of patients had favorable outcomes and 43 percent were functionally independent. Thirteen patients (3.3 percent) experienced symptomatic intracerebral

hemorrhage, including seven deaths. Protocol violations were reported in 127 (32.6 percent) patients and included: 1) treatment with tPA more than three hours after symptom onset in 13.4 percent; 2) treatment with anticoagulants within 24 hours of tPA administration in 9.3 percent; and, 3) tPA administration despite systolic blood pressure exceeding 85 mm Hg in 6.7 percent. This study suggests that favorable clinical outcomes and low rates of symptomatic intracerebral hemorrhage can be achieved using tPA for stroke treatment. [60]

- Katzan et al published the results of a study to assess the rate of tPA use, the incidence of symptomatic intracerebral hemorrhage and in-hospital outcomes in 29 hospitals in the Cleveland, Ohio metropolitan area (July 1997 through June 1998). Out of a total of 3,948 patients admitted with a primary diagnosis of ischemic stroke, 70 (1.8 percent) received tPA. Of those 70 patients receiving intravenous tPA, 11 (15.7 percent) had a symptomatic intracerebral hemorrhage (six fatal) and 35 (50 percent) had deviations from the national treatment guidelines. In-hospital mortality was significantly higher among patients treated with tPA (15.7 percent) compared to those without tPA (5.1 percent). [66]
- A study at a busy teaching hospital included 68 consecutive patients with acute ischemic stroke who were treated with intravenous tPA within three hours of symptom onset by attending neurologists. Of these patients, 26 (38 percent) made a full recovery and 39 (57 percent) made a recovery with some level of independence. The risk of symptomatic hemorrhage was found to be similar to that in the randomized trials. Eleven of the patients were treated in violation of the protocol and had a lower probability of full neurologic recovery and a higher probability of symptomatic hemorrhage and death compared to the 57 patients treated within the NINDS guidelines. The authors concluded that treating patients who with intravenous tPA who violate the NINDS guidelines exposes them to excess risk with no observable benefit. [65]
- A recent placebo-controlled study provided evidence of a sustained benefit at one year from systemic thrombolysis in patients with acute ischemic stroke. Between March 1996 and July 1998, 150 consecutive patients with acute ischemic stroke were treated with intravenous Alteplase in accordance with AHA guidelines. Patients were followed up for one year after treatment. Baseline patient characteristics and complications were comparable to those found in the NINDS study. The overall rate of recurrent stroke was 6.6 percent and TIA was 3.3 percent at one year. Six patients (four percent) died after the first three months, none of them due to recurrent stroke, and five were already severely disabled. These observations further encourage the routine use of tPA for the treatment of acute ischemic stroke in strict accordance with AHA guidelines. [74]

A supplement to the American Heart Association's Guidelines for the Management of Patients with Acute Ischemic Stroke focusing on thrombolytic therapy was published in 1996. [5] In addition, a Practice Advisory was published by the American Academy of Neurology (AAN) [50] which recommended the use of the thrombolytic therapy selection criteria for patients from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (NINDS) study. [33] The AAN Practice Advisory also recommended the use of the treatment protocol from the NINDS study.

Possible Emerging Therapies

Recently, attention has been focused on r-tPA for intra-arterial administration. Data are still limited regarding the intra-arterial dose, efficacy and safety profile of this agent. A small prospective study of eight patients referred for intra-arterial thrombolysis was published in August 2000. [81] Each patient was considered a poor candidate for intravenous therapy by the treating neurologist. Intervals from

presentation to treatment ranged from one to eight hours. A maximum total dose of 40 mg of r-tPA was administered intra-arterially. Angiograms were obtained after each 10 milligrams of r-tPA and responses were graded. After administration of the r-tPA, neurological improvement was observed in four patients and asymptomatic intraparenchymal hemorrhage was observed on CT scan in two patients at 24 hours. This study suggests that intra-arterial r-tPA in doses up to 40 milligrams is relatively safe. [81]

Ancrod, a defibrinogenating agent made from the venom of the Malaysian pit viper, has been strudied as a possible treatment for acute stroke. The results of the Stroke Treatment with Ancrod Trial (STAT), a randomized, placebo-controlled trial conducted, were published in May 2000. [95] There were forty-eight medical centers, primarily community hospitals, in the United States and Canada and a total of 500 patients with acute or progressing ischemic deficits included in the trial. Patients were randomly assigned to receive ancrod (n=248) or placebo (n=252) as a continuous 72-hour infusion beginning within three hours of stroke onset, followed by infusions for approximately one hour at 96 and 120 hours. More patients in the ancrod group (42.4 percent) than the placebo group (34.4 percent) achieved favorable functional status. Mortality was not different between the two groups. There was a trend toward more symptomatic intracranial hemorrhages in the ancrod group compared to placebo (5.2 percent versus two percent), as well as a significant increase in asymptomatic intracranial hemorrhages (19 percent versus 10.7 percent). [95] These results of this trial are controversial and have been discussed in an editorial [97] and subsequent letters to the editor of the *Journal of the American Medical Association.* [96,98]

DVT Prophylaxis

All stroke patients should be evaluated for the possible presence of deep vein thrombosis (DVT), as it is an important cause of pulmonary embolism, and therefore, morbidity and mortality following a stroke:

- A meta-analysis from 1997 found that estimates of the frequency of DVT in untreated patients ranged from 20-75 percent. The wide range depended on the methods used to detect DVT and on the degree of lower limb paralysis. Pulmonary embolism was found to be the third most common cause of death in stroke patients and occurred in 1-2 percent of patients who do not receive prophylactic treatment. [57]
- A community study from Massachusetts found that pulmonary embolism was listed as a contributing cause of death in 43 percent of those patients with a first episode of thrombo-embolism. [56]
- In their Post-Stroke Rehabilitation Guidelines, the AHRQ found that as many as ten percent of deaths from stroke have been attributed to pulmonary embolism and the risk is increased by the paralysis of a limb and resulting immobility. [17]
- The guidelines for prevention of venous thromboembolism published in *Chest* in 1992 reported that thromboembolism can occur in as many as 47 percent of untreated patients. [10]

Recommended therapy to prevent thromboembolism in stroke patients stresses the use of low-dose heparin and low molecular weight heparin as preferred treatments. Warfarin and intermittent pneumatic compression devices are also considered effective. [17] The results of a recent randomized trial of graded compression stockings for prevention of DVT after acute stroke found that the stockings

produced a reduction in DVT incidence comparable to those of other patient groups, but the reduction was not statistically significant. [75] Prevention of DVT in stroke should also include early mobilization. [17, 58]

Changing Clinical Processes

In the first nationally based survey of physician practices relating to secondary and tertiary prevention of stroke by Goldstein et al., a large amount of variability in practice patterns was found to exist among physicians treating older patients at risk for stroke and TIA. This variability may be due to lack of standardization of testing procedures, as well as a knowledge gap that could be addressed by targeted physician education efforts and systematic changes in procedures.[23]

Along the same lines, a recent study conducted in Canada (the Saskatchewan Clinical Stroke Prevention Project) will offer relevant input into this project when the results are published in the future.[25] In this study, 24 physicians in three practices are participating in a staged series of educational interventions over two years, targeted at enhancing their management of smoking, TIA/stroke, atrial fibrillation and hypertension. It is hypothesized that with the following intervention components, physicians will implement preventive techniques into their practices that will be measurable in terms of process as well as impact: a seminar, printed materials, a one-to-one case discussion (academic detailing), a self-documented chart audit and changes to the office system.

According to Gottlieb, these very specific, directed efforts to change physician behavior are necessary because the efficacy demonstrated in clinical trials does not necessarily translate into effectiveness in practice without taking into consideration the differences in patient populations between the two settings and the fact that therapeutic interventions are often more successful in the clinical trials. [24] This specific study found that the greater prevalence of comorbidities in the community setting led to a greater overall risk of thromboembolism and bleeding complications than in the clinical trials. A study out of Minneapolis, however, discovered that there were positive changes in the stroke and TIA management practices of community and academic neurologists in response to the publication of CEA randomized trials. [37] This finding indicates that physicians do respond to the results of scientific research and are able to interpret them and make them relevant to community practice. [21]

A growing body of scientific literature in the United States and abroad has been dedicated to the establishment of stroke centers as a method of achieving the system change that is required to improve stroke care for all stroke patients, but specifically those that are eligible for thrombolytic therapy. [85, 86, 89, 90] This approach mirrors the approach used for establishing trauma centers which were organized after studies found that many lives were being lost due to the frequent lack of necessary medical infrastructure needed to stabilize and treat patients with severe trauma. [82]

A consensus statement from the Brain Attack Coalition (BAC) , a multidisciplinary group of representatives from major professional organizations involved in delivering stroke care, determined that two levels of stroke centers should be established: 1) a primary stroke center to stabilize and provide emergency care; and 2) a comprehensive stroke center to provide complete care to patients experiencing the most complex strokes requiring specialized testing and interventions. The BAC identified the following as key elements of stroke centers: multidisciplinary acute stroke teams, dedicated stroke units, specific care protocols and integrated emergency response systems. [82]

Important support services include availability and interpretation of CT scans 24 hours every day and rapid laboratory testing capability. In addition, administrative support, strong leadership and continuing education are important elements of stroke centers. The authors of this consensus statement believe that adoption of stroke centers may increase the use of appropriate diagnostic and therapeutic modalities and reduce complications related to stroke. [82]

The results of several recent studies support the opinion that the establishment of a stroke center has the potential to improve care:

- A hospital in Calgary, Canada organized acute stroke care into a multidisciplinary team which included the stroke team, departments of neurology, diagnostic imaging and emergency medicine, the stroke unit and emergency medical services. Aspects of this effort included public education about the symptoms of stroke, training for paramedics regarding quick stroke assessment, and training for emergency department personnel regarding triage of suspected stroke as an emergency. After three years, their efforts have resulted in improved patient outcomes, shorter times from symptom onset to treatment and acceptable adverse event rates. Areas for continued improvement include door-to-needle time and broader education of the public about the symptoms of acute stroke. [83]
- A teaching hospital in Ireland reported on a three-year audit of the first acute stroke service. This study was conducted prospectively on 193 patients admitted to the acute stroke unit from July 1996 to June 1999. In years one, two and three, respectively, a reduction in mortality (from 19 percent to 15 percent to nine percent) was observed. Likewise, an increasing percentage of patients discharged home was noted (from 55 percent to 64 percent to 68 percent). [84]
- Identification of the availability of stroke services in a given geographic area is the logical first step to establishing a stroke center. Goldstein et al studied the availability of such services in North Carolina through the use of a one-page survey. Some of the data categories included diagnostic studies, stroke services (i.e., neurologist on staff, tPA protocol in place) and organizational features (i.e., stroke care map, organized stroke team). [87]
- A single-blind, randomized trial was undertaken in Britain to follow 457 acute stroke patients randomly assigned to a stroke unit, general ward with stroke team support or home stroke care within 72 hours of stroke onset. Outcome was assessed at three, six and 12 months. Mortality or institutionalization at one year were lower in patients on a stroke unit (14 percent) than those receiving care from a stroke team (30 percent) or home care (24 percent). [88]
- Indredavik et al published three articles related to results of their randomized, controlled trial in Europe. They looked at the effect stroke unit care had on outcomes for 110 patients with acute stroke that were allocated to a stroke unit or a general ward. After five to ten years of follow-up, patients receiving stroke unit care had less mortality and morbidity, were functioning more independently and enjoyed a higher quality of life. [91-93]
- A quasi-randomized controlled study in Norway tested the hypothesis that a stroke unit increases one-year and 18-month survival rates. The study included 802 patients admitted to a hospital with acute stroke between January 1993 and February 1995. Each patient was allocated to a stroke unit or a general ward. One-year survival among patients treated in the stroke unit was 70.6 percent compared to the general ward patients at 64.6 percent. Eighteen month survival rates were 65 percent and 58 percent respectively. [94]

A study from Duke University was able to measure positive change in the practices of their neurologists and neurology house officers between 1986 and 1994 as it related to the use of aspirin, heparin and warfarin in patients with TIAs. [22] This change to less intense anticoagulant use was based upon the dissemination of clinical research study results that clearly demonstrated the safety and efficacy of low-intensity anticoagulation for preventing strokes. The study found that most of the respondents were no longer using heparin IV boluses, the mean PT/PTT had fallen significantly, and most respondents were using a dose of 325 mg of aspirin per day.

Clinical pathways have been shown to be an effective system change when implemented as part of a quality improvement effort. [53] Results of a successful process change effort in a community hospital in Mississippi were published recently and highlight the use of a stroke clinical care pathway to improve rates on quality indicators. This hospital was one of five that participated with the Information and Quality Healthcare (Mississippi PRO) in a quality improvement project in 1994. Baseline measurement involved retrospective review of the records of 73 patients meeting the inclusion criteria and discharged in 1994. In January 1995 a clinical pathway for stroke was implemented. Results of the baseline analysis indicated that almost all of the patients in the study had a CT as part of their stroke evaluation and 76 percent of these scans were performed within 24 hours. Following application of the clinical pathway, there was an increase to 95 percent in those with a CT scan within 24 hours. There was a significant increase in the use of DVT prophylaxis at remeasurement, mostly seen in the use of subcutaneous heparin and graduated compression stockings. In the baseline study, 22 percent of the stroke patients were treated acutely for hypertension and 94 percent of these received sublingual nifedipine. Remeasurement indicated that no patients were treated emergently for hypertension. In addition, there was an increase in the number of patients receiving antithrombotics at discharge, although the increase was not significant. It is also important to note that the length of stay was decreased and there was no significant increase in hospital costs. The authors concluded that when applied properly, clinical pathways can effectively mobilize hospital resources, maximize quality of care and minimize costs. [68]

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